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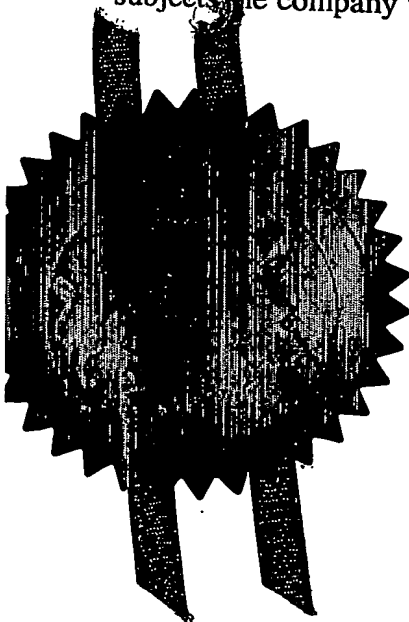
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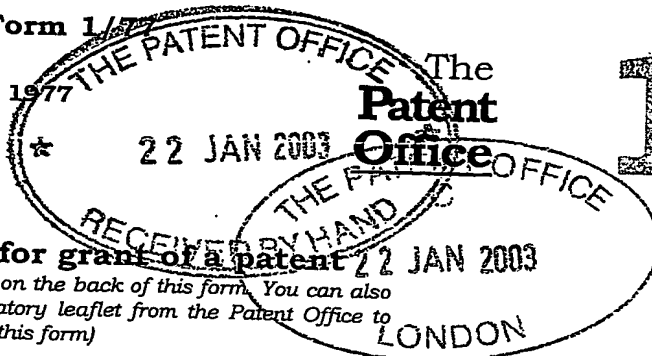
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Dated 19 November 2003



1/77

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1. Your reference **G-32855P1/BCK 9934**

2. Patent application number **22 JAN 2003** **0301471.9**  
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3. Full name, address and postcode of the or of each applicant **BIOCHEMIE GESELLSCHAFT MBH**  
(underline all surnames) **A-6250 KUNDL, TIROL**  
**AUSTRIA**

Patent ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation **AUSTRIA**

**08365158001**

4. Title of invention **Organic compounds**

5. Name of your agent (if you have one) **Novartis Pharmaceuticals**  
"Address for service" in the United **UK Limited**  
Kingdom to which all correspondence **Patents and Trademarks**  
should be sent **Wimblehurst Road**  
(including the postcode) **Horsham West Sussex**  
**RH12 5AB**

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Country	Priority application number (if you know it)	Date of filing (day/month/year)

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Number of earlier application	Date of filing (day/month/year)

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a) any applicant named in part 3 is not an inventor, or

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Date

B. A. Yorke & Co.

B.A. Yorke & Co.

22 January 2003

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Mrs. J. Crook  
020 8560 5847

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### Organic Compounds

The present invention relates to solid pharmaceutical compositions comprising Ramipril with a suitably low water content, and processes for preparing said compositions.

#### **Description of the invention**

The present invention relates to the discovery of stable Ramipril pharmaceutical compositions and to methods making such compositions. Stability is the most important aspect of a pharmaceutical composition. In particular for Ramipril degradation occurs via two pathways the hydrolysis to Ramipril-diacid (Impurity E described in European Pharmacopoeia) and the cyclization to Ramipril-diketopiperazide (Impurity D described in European Pharmacopoeia).

Information published in EP 0 314 878, data generated on stress stability testing of commercial Ramipril formulations (e. g. Delix<sup>®</sup>) and data generated internally during development on own formulations reveal that the major instability arises from the formation of the diketopiperazide. Enclosed table shows the level of Ramipril-diketopiperazide and Ramipril-diacid after storage of Delix<sup>®</sup> 1.25mg (batch number C-423; originating from the German market) for 8 weeks at 40° C/75% relative humidity (RH).

Ramipril-Diketopiperazide [%]	Ramipril-diacid [%]
2.16	0.16

The European Pharmacopoeia states an encouraging limit of 0.5% for diketopiperazide. Preferably the stability of a commercial composition is such that, after 3 months, preferably 6 months storage in a controlled environment of 40° C/75% RH, the loss of the active principle is less than 5% and the increase of impurities is preferably double the amount stated in the relevant Pharmacopoeia, in the case of Ramipril the European Pharmacopoeia for the relevant impurity in the active principle. In the particular case of Ramipril the level of diketopiperazide should preferably not exceed 1.0% after storage at 40° C/75% RH for 3 months, preferably 6 months.

In patent EP 0 314 878 it is well documented that Ramipril formulations manufactured by standard technologies show considerable degree of instability. Hoechst did manage to

overcome the stability problem by applying a commercially expensive and technically complicated technology (coating of Ramipril with a polymer prior to compression). We surprisingly found that these prior art stability problems can be overcome applying pharmaceutical standard technologies when properly controlling/limiting water content in the final formulation. It was found that stability with the proposed formulations and processes is even improved over the currently marketed commercial formulations of Ramipril. It was surprisingly found that other prior art approaches for stabilisation of ACE inhibitors (formulations with acid-donors, formulations with sodium bicarbonate) did not reveal a sufficiently stable formulation except when water content was properly controlled concurrently. In addition it was surprisingly found that testing formulations with controlled water content not applying prior art approaches prove sufficiently stable as well. Whereas the focus of the trials was put on tablet formulations the principal could be demonstrated to be as well suitable for capsules and is considered to be suitable for sachets as well.

Whereas moisture has been linked to the hydrolysis of ACE-inhibitors to the respective ACE-inhibitor-diacids – which in the case of Ramipril has never been a challenge as Ramipril-diacid is not formed in significant amounts even when using standard excipients and pharmaceutical technologies – it was surprisingly found that the underlying mechanism of cyclization of Ramipril to the Ramipril-diketopiperazide is directly linked to the presence of moisture in the formulation.

Diketopiperazides are formed by cyclization within the dipeptide moiety of ACE inhibitors in particular for the Ramipril between the alanine and the proline moiety. Prior art approaches focused on inhibition of this cyclization by blocking free valences with e. g. acid-donors or decreasing susceptibility of the carboxylic acid moiety of the proline towards cyclization by converting it into an ion e. g. by addition of carbonates or other buffer substances. The current approach bases on the fact that cyclization can only occur if the configuration about the dipeptide-peptide changes from the trans to the cis position.

This interconversion can only occur when Ramipril is in solution. The water present in the active ingredient and/or the excipients and the water taken up from the environment is sufficient to achieve a microenvironment where Ramipril can partially dissolve and interconvert from the trans- to the cis-rotamer. By exclusion of water this interconversion and the consecutive cyclization can be prohibited.

Therefore the invention covers a solid pharmaceutical composition containing  
(a) Ramipril and/or a pharmaceutical acceptable salt thereof and  
(b) one or more pharmaceutical excipients,

wherein the composition has a suitably low water content.

Solid pharmaceutical compositions according to the invention include tablets, capsules, capsulets and sachets. Tablets may be suitably coated (film coated tablets, drages). This coat might represent an additional barrier towards moisture. Capsule formulations may cover both soft and hard capsules.

The form of the Ramipril and/or a pharmaceutical acceptable salt thereof is not particularly limited and includes all pharmaceutically acceptable anhydrides, solvates, hydrates, crystalline and amorphous forms. The amount of Ramipril is not particularly limited and comprises any amount that is pharmaceutically effective.

Low water content can be achieved by a combination of suitable excipients showing low water content, process parameters that prohibit uptake of moisture during manufacture and proper packaging material that prohibits uptake of moisture during storage of the finished dosage form over shelf life. Suitable excipients with low water content are most preferably special grades of microcrystalline cellulose (e. g. Avicel PH 112), starch (e. g. Starch 1500 LH), silicon dioxide (e. g. Syloid AL-1 FP), calcium phosphate (e. g. Dicalfos A) but should not be limited to the excipients mentioned herein but extended to all declared low humidity excipients including diluents, binders lubricants, disintegrants colorants, etc.. Even when applying excipients with low levels of water the blend and final formulation is susceptible to take up moisture during manufacture and during storage. Accumulation of humidity during processing can be properly limited by performing the manufacture under controlled environmental conditions. Preferred is the manufacture in an environment of less than 35% RH. Accumulation of moisture during storage can be properly avoided by using packaging materials known to be reasonably tight to penetration of humidity. Packaging materials preferred are containers including lid composed of polyethylene and/or polypropylene and/or glass and or blisters or strips composed of aluminium or high density polyethylene.

The water content in the composition is determined by loss-on-drying (LOD) and/or Karl-Fischer (KF)-analysis as it is understood by workers skilled in the art. For all data cited in this application below mentioned methods were used. Out of these two methods KF is known to be more reproducible and specific. Thus KF is the preferred method to assess water content in pharmaceutical formulations.

LOD: For tablet formulations tablets are crushed to powder in a mortar with a pestle. For capsule or sachet formulations the content of the capsule or sachet is emptied out. The loss on drying is determined on a moisture balance e.g. Mettler LP 16 using approximately 1.0 g of the sample. The mixture is evenly spread on the weighing plate of the moisture balance. The weighing plate is preheated to 80°C and the mixture is then dried for 15 minutes at 80° C.

KF: For tablet formulations tablets are crushed to powder in a mortar with a pestle. For capsule or sachet formulations the content of the capsule or sachet is emptied out. The water content is determined with an automated KF apparatus e. g. Metrohm 784 KFP Titrino using conventional Karl Fischer reagent on a sample of using 0.1 g of the sample.

Manufacturing the product with conventional excipients results in a considerably high decrease in assay and increase in diketopiperazide. This prior art instability is properly documented in EP 0 317 878. Hoechst attributed the increase of diketopiperazide up to 22.8% after 6 months at 40° C and the decrease in assay down to 20% after 6 months at 40° C to mechanical stress and concluded to coat the active principle in order to protect it from mechanical stress.

As reference for formulations manufactured with conventional excipients and showing normal levels of water content commercial formulations of Ramipril can be taken. Results on commercial formulations of Ramipril achieved with LOD and KF are presented in enclosed tables.

Results of originator formulation with K.F.

Product Name	Batch No.	Strength	Formulation	Country	Water content [weight-%]
Delix®	40A428	2.5mg	Tablets	Germany	8.00

Delix <sup>®</sup>	40A475	5mg	Tablets	Germany	7.34
Delix <sup>®</sup> Protect	1W425	10mg	Tablets	Germany	7.24
Tritace <sup>®</sup>	W245	1.25mg	Capsule	Austria	11.07
Tritace <sup>®</sup>	A232	2.5mg	Capsule	Austria	10.03
Tritace <sup>®</sup>	A228	5mg	Capsule	Austria	9.95
Tritace <sup>®</sup>	W429	10mg	Tablets	Austria	7.78

## Results of originator formulation with LOD

Product Name	Batch No.	Strength	Formulation	Country	Water content [weight-%]
Delix <sup>®</sup>	40A428	2.5mg	Tablets	Germany	6.37%
Delix <sup>®</sup>	40A475	5mg	Tablets	Germany	6.11%
Delix <sup>®</sup> Protect	1W425	10mg	Tablets	Germany	5.97%
Tritace <sup>®</sup>	W245	1.25mg	Capsule	Austria	9.52%
Tritace <sup>®</sup>	A232	2.5mg	Capsule	Austria	8.68%
Tritace <sup>®</sup>	A228	5mg	Capsule	Austria	8.40%
Tritace <sup>®</sup>	W429	10mg	Tablets	Austria	6.70%

This type of formulation is only stable when Ramipril is separated by a polymeric barrier from the water bearing excipients (formulations described in EP 0 317 878 and "Rote Liste"). The effect of the barrier was attributed by Hoechst to reduced mechanical stress during compression but is according to our surprising findings as well attributable to minimising contact of Ramipril with water throughout storage over shelf life. Tight contact between Ramipril and a water bearing excipients is required to allow partial dissolution of Ramipril consecutively followed by cyclization to the diketopiperazide.

Stability results generated on example 3 and 4 are consistent with findings of EP 0 317 878 and properly support that Ramipril formulations showing conventional levels of moisture can, if at all, be stabilised by preventing interaction of Ramipril with water. A considerably stable formulation however can easily be achieved when keeping LOD low.

Assay of Ramipril [%]		
	Example 3 (LOD 2.71)	Example 4 (LOD 6.60)
Initial	101.11	97.85
1 week	102.23	90.73
2 weeks	99.90	-
4 weeks	101.21	-

Besides choosing excipients with low water content, performing the manufacture in an environment of sufficiently low relative humidity is essential as demonstrated in enclosed example. A blend manufactured according to example 1 was exposed to well defined



environmental conditions of relative humidity at ambient temperature for up to 6 hours. Only when maintaining the relative humidity at approximately 30% the initial load with moisture could be maintained. At ambient humidity levels (50 – 60%) the blend has significantly taken up moisture already after 2 hours. Considering that normal processing times for pharmaceutical products range from 8 hour up to one week control of this parameter becomes essential.

Time [h]	30% RH		50-60% RH		70% RH	
	LOD [weight-%]	KF [weight-%]	LOD [weight-%]	KF [weight-%]	LOD [weight-%]	KF [weight-%]
2	3.21	4.09	5.31	6.60	5.79	6.87
4	3.19	5.33	5.41	6.62	7.49	7.70
6	3.51	4.24	5.91	6.67	7.90	8.46

The third factor to control humidity in the final product is to prevent uptake of moisture during storage. It is well established that commercialising products in the containers including lid made of polypropylene and/or polyethylene and/or glass or in blisters and/or strips composed of aluminium or high density polyethylene prevents them from taking up moisture during storage over shelf life. Enclosed example shows uptake of moisture of tablets manufactured according to example 1 and stored at 40° C/75% RH in various packaging materials. Whereas trilaminate (PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm) blister packs reach a level of saturation already after 1 months, polypropylene containers with polyethylene lid and Alu/Alu strips show no increase in water content up to 6 months.

Time [months]	LOD [weight-%]		
	PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister pack	Alu/Alu 40 µm strip pack	Polypropylene container with polyethylene lid
0	3.29	3.29	3.29
1	5.70	3.51	-
2	5.79	2.61	-
3	-	2.30	2.81
6	-	1.93	2.79

Applying above mentioned principles reliably yield products with water contents of preferably less than 4.0 weight-%, most preferably less than 3.0 weight-% as determined by LOD or less than 5.5 weight-%, most preferably less than 4.5 weight-% as determined by KF. By

applying adequate packaging technologies the moisture content in the formulation can be maintained adequately low.

It was surprisingly found that formulations applying prior art approaches did not prove the anticipated level of stability except content of water was adequately controlled. In example 1 formulations were prepared with a hydrochloric acid donor (glycine hydrochloride) as described in EP 0 468 929. The pharmaceutical compositions were put on accelerated stability in different packaging materials. Results are shown in enclosed table.

Package	Alu/Alu 40 µm strip pack			PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister pack		
Time [months]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]
0	3.19	98.68	0.12	3.19	98.68	0.12
2	2.91	97.87	0.12	5.81	65.63	9.68

It was surprisingly observed that these pharmaceutical compositions only prove sufficiently stable under accelerated testing conditions when water content is low. Concurrently with increase of moisture, degradation to diketopiperazide. From these results it is obvious that formulations with an initial LOD of more than 5% prove insufficiently stable.

### Working Examples:

#### Example 1:

During the manufacturing process environmental conditions of 30% RH/ 30°C. are kept. Milled glycine hydrochloride (0.300kg) is dry-mixed with Ramipril (0.125kg), microcrystalline cellulose (Avicel PH112; 7.125kg), precipitated silicon dioxide (Syloid AL-1-FP; 0.800kg) and pregelatinised starch (Starch 1500 LM; 0.450kg), and the resulting mixture is dry-mixed with glycerol dibehenate (Compritol ATO 888; 0.200kg) and compressed to yield 100,000 tablets containing 1.25mg Ramipril each.

For enclosed stability investigation the tablets are immediately packaged into PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister packs and Alu/Alu 40 µm strips. The samples are put on stability at 40° C/75% RH. The LOD of the tablets after manufacture is 3.19 weight-%.

Assay values of Ramipril and diketopiperazide are generated with suitable HPLC methods. A reference method the HPLC method described in the European Pharmacopoeia 2001 (monograph 'Ramipril') can be taken.

Package	Alu/Alu 40 µm strip pack			PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister pack		
Time [months]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]
0	3.19	98.68	0.12	3.19	98.68	0.12
2	2.91	97.87	0.12	5.81	65.63	9.68

Example 1 demonstrates that pharmaceutical compositions prepared with glycine hydrochloride prove sufficiently stable under accelerated testing conditions when water content is low but prove unstable when water content increases to normal levels of moisture within pharmaceutical formulations.

#### Example 2:

During the manufacturing process environmental conditions of 30% RH/ 30°C are kept. Milled glycine hydrochloride (0.300kg) is dry-mixed with Ramipril (0.500kg), microcrystalline cellulose (Avicel PH112; 29.36kg), precipitated silicon dioxide (Syloid AL-1FP; 3.200kg), pregelatinised starch (Starch 1500 LM; 1.800kg), and Iron Oxide Red (0.040kg) and the resulting mixture is dry-mixed with glycerol dibehenate (Compritol ATO 888; 0.800kg) and compressed to yield 100,000 tablets containing 5mg Ramipril each, which are immediately packaged into PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister packs, Alu/Alu 40 µm strips and polypropylene container with polyethylene lid. The LOD of the tablets after manufacture is 3.19 weight-%.

Package	PVC/PE/PVDC 250µ/25µ/90 gsm and aluminium foil 20 µm blister pack			Alu/Alu 40 µm strip pack			Polypropylene container with polyethylene lid		
Time [months]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]	LOD [weight-%]	Ramipril [%]	Diketopiperazide [%]
0	2.41	99.78	0.14	2.41	99.78	0.14	2.41	99.78	0.14
1	3.97	99.56	0.09	1.90	100.88	0.12	-	-	-
2	4.71	92.54	3.89	2.11	101.61	0.18	-	-	-
3	-	-	-	1.50	99.34	0.16	2.19	99.43	0.15
6	-	-	-						

Example 2 supports the findings of example 1. In particular example 2 demonstrates that low humidity compositions maintain levels of diketopiperazide far below the limit of 0.5% as stated in the European Pharmacopoeia and far below the results obtained for commercial Ramipril formulation (Delix® 1.25mg batch number C-423; originating from the German market; 2.16% diketopiperazide).

### Example 3:

In analogy to example 1 aluminium strips containing tablets with the following composition are prepared: Ramipril (1.25mg), microcrystalline cellulose (Avicel PH112; 50.32mg), precipitated silicon dioxide (Syloid AL-1-FP; 4.6mg), lactose (Lactose DCL-21; 37mg), glycerol dibehenate (Compritol ATO 888; 1.83mg) at laboratory scale at ambient environmental conditions. The tablets are packaged into Alu/Alu 40 µm strips and put on stability at 40° C/75% RH. The LOD of the tablets after manufacture is 2.71 weight-%.

	Assay of Ramipril [%]
Initial	101.11
1 week	102.23
2 weeks	99.90
4 weeks	101.21

Example 3 demonstrates that pharmaceutical compositions prepared with suitable excipients and not containing prior art stabilising agents do not show any significant degradation over 4 weeks when stored under accelerated testing conditions.

### Example 4:

In analogy to example 1 aluminium strips containing tablets with the following composition are prepared: Ramipril (1.25mg), starch (Starch 1500; 20.32mg), silicon dioxide (Aerosil 200; 1.00mg), lactose (Lactose DCL-21; 78.00mg), Ac-Di-Sol (4.00mg) and Sterotex (1.80mg) at laboratory scale at ambient environmental conditions. The tablets are packaged into Alu/Alu 40 µm strips and put on stability at 40° C/75% RH. The LOD of the tablets after manufacture is 6.60 weight-%.

	Assay of Ramipril [%]
Initial	97.85
1 week	90.73
2 weeks	-
4 weeks	-

Example 4 demonstrates that pharmaceutical compositions prepared with conventional excipients and not containing prior art stabilising agents do not prove stable when stored under accelerated testing conditions. Already after one week of storage the content of Ramipril has decreased for more than 5%.

#### Example 5:

At laboratory scale at ambient environmental conditions capsules containing Ramipril (1.25mg) and starch (Starch 1500; 138.75mg) are prepared by dry-mixing of Ramipril and Starch 1500 and filling the blend into conventional hard gelatine capsules. The capsules are packaged into Alu/Alu 40 µm strips and put on stability at 40° C/75% RH. The LOD of the capsules is 8.27 weight-%.

	Diketopiperazide [%]
Initial	0.15
1 week	0.81
2 weeks	-
4 weeks	2.14
6 weeks	3.93

Example 5 demonstrates that capsule formulations showing a conventional level of water content do not prove stable when stored under accelerated testing conditions. After 6 weeks of storage at accelerated testing conditions the content of diketopiperazide has increased up to 4%.

#### Example 6:

In analogy to example 5 aluminium strips containing capsules with the following composition are prepared: Ramipril (1.25mg), starch (Starch 1500 LM; 37.00mg) and perlitol (148.75mg) are mixed and the blend is filled into conventional capsules at laboratory scale at ambient environmental conditions. The capsules are packaged into Alu/Alu 40 µm strips and put on stability at 40° C/75% RH. The LOD of the capsules 5.79 weight-%.

	Diketopiperazide [%]
Initial	0.19
1 week	0.81
2 weeks	-

4 weeks	1.23
6 weeks	3.01

Example 6 support the findings of example 5. A LOD above 5 weight-% does not allow a sufficiently stable formulation. A significant trend toward stabilisation with decreased moisture load is obvious.

**Example 7:**

In analogy to example 5 aluminium strips containing capsules with the following composition are prepared: Ramipril (1.25mg), microcrystalline cellulose (Avicel PH 101; 71.48mg), starch (Starch 1500; 20.47mg), and arginine (1.80mg) are mixed and the blend is filled into conventional capsules at laboratory scale at ambient environmental conditions. The capsules are packaged into Alu/Alu 40 µm strips and put on stability at 40° C/75% RH. The LOD of the capsules 3.24 weight-%.

	Diketopiperazide [%]
Initial	0.71
1 week	0.23
2 weeks	-
4 weeks	0.32

Example 7 demonstrates that capsule formulations showing a low level of water content prove considerably stable towards cyclization of the active principle to diketopiperazide when storage at accelerated testing conditions. Example 5, 6 and 7 demonstrate that the principle of stabilising Ramipril formulations by excluding moisture in the formulation applies for capsule formulations as well. The assay of Ramipril as well remains above 95%.

**Claims**

1. Solid pharmaceutical composition comprising
  - (a) an effective amount of Ramipril and/or a pharmaceutical acceptable salt thereof and
  - (b) one or more pharmaceutically acceptable excipients, wherein the composition has a suitably low water content.
2. Composition according to claim 1, wherein the water content is less than about 4.5 weight-% measured by Karl-Fischer-analysis.
3. Composition according to claim 1, wherein the water content is less than about 5.5 weight-% measured by Karl-Fischer-analysis.
4. Composition according to any of the preceding claims, wherein Ramipril and/or a pharmaceutical acceptable salt thereof is in form of pharmaceutically acceptable anhydrate, solvate and/or, hydrate and/or in crystalline and amorphous form.
5. Composition according to any of the preceding claims, wherein the pharmaceutical composition is a tablet.
6. Composition according to claim 5, wherein the tablet is suitably coated to generate a filmcoated tablet and/or a drage.
7. Composition according to claim 1 – 4, wherein the pharmaceutical composition is a capsule.
8. Composition according to claim 1 – 4, wherein the pharmaceutical composition is a sachet.
9. Composition according to any of the preceding claims, wherein excipients are special low humidity grades - as it is understood by workers skilled in the art - of - including but not limited – pharmaceutically acceptable diluents, binders lubricants, disintegrants and colorants.
10. Composition according to claim 9, wherein one of said excipients is microcrystalline cellulose.
11. Composition according to claim 1 - 9, wherein one of said excipients is Avicel PH 112.
12. Composition according to claim 9, wherein one of said excipients is starch.
- ~~13. Composition according to claim 1 - 9, wherein one of said excipients is Starch 1500~~  
LH.

14. Composition according to claim 9, wherein one of said excipients is silicon dioxide.
15. Composition according to claim 1 - 9, wherein one of said excipients is Syloid AL-1 FP.
16. Composition according to claim 9, wherein one of said excipients is calcium phosphate.
17. Composition according to claim 1 - 9, wherein one of said excipients is Dicafos A.
18. Composition according to any of the preceding claims where one or more excipients are dried prior to use or throughout the process to achieve the required level of humidity.
19. Process for the preparation of a composition according to any of the preceding claims, wherein environmental conditions during manufacture are maintained at a relative humidity equal or less than 35% at ambient temperature.
20. Process for the preparation of a composition according to claim 1 - 18, wherein environmental conditions during manufacture are maintained at a relative humidity equal or less than 35% at equal or less than 30° C.
21. Process according to any of the preceding claims, wherein the pharmaceutical composition is packaged into a suitably tight packaging material for commercialisation.
22. Process according to claim 21, wherein the packaging materials is a container including lid composed of polyethylene and/or polypropylene and/or glass.
23. Process according to claim 21, wherein the packaging material is a strip or blister pack composed of aluminium which might be suitably coated or high density polyethylene.



**Abstract**

The present invention relates to solid pharmaceutical compositions comprising Ramipril with a suitably low water content, and processes for preparing said compositions.

PCT Application

PCT/EP2004/000456

